REVIEW

Management of fever and neutropenia in paediatric cancer patients: room for improvement?

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Purpose of review
Fever and neutropenia is the most common complication in the treatment of childhood cancer. This review will summarize recent publications that focus on improving the management of this condition as well as those that seek to optimize translational research efforts.

Recent findings
A number of clinical decision rules are available to assist in the identification of low-risk fever and neutropenia however few have undergone external validation and formal impact analysis. Emerging evidence suggests acute fever and neutropenia management strategies should include time to antibiotic recommendations, and quality improvement initiatives have focused on eliminating barriers to early antibiotic administration. Despite reported increases in antimicrobial resistance, few studies have focused on the prediction, prevention, and optimal treatment of these infections and the effect on risk stratification remains unknown. A consensus guideline for paediatric fever and neutropenia research is now available and may help reduce some of the heterogeneity between studies that have previously limited the translation of evidence into clinical practice.

Summary
Risk stratification is recommended for children with cancer and fever and neutropenia. Further research is required to quantify the overall impact of this approach and to refine exactly which children will benefit from early antibiotic administration as well as modifications to empiric regimens to cover antibiotic-resistant organisms.

Keywords
cancer, child, fever and neutropenia, review, risk stratification

INTRODUCTION

In children with cancer, fever and neutropenia is the leading cause of emergency department presentation and unplanned hospital admission [1,2▪]. Management traditionally involves admission to hospital for intravenous antibiotics until resolution of fever and recovery of neutrophil count. However, children with fever and neutropenia are a heterogeneous group with varying risk of severe infection or medical complications and this treatment approach is increasingly recognized as excessive for low-risk episodes [3]. Clinical decision rules (CDRs) are available to assist in risk stratification although few centres have adopted these into routine practice [4,5]. Furthermore, most have focused on the identification of low-risk fever and neutropenia and little is available to assist in the early recognition of conditions associated with significantly higher morbidity and mortality, such as severe sepsis and infection with antimicrobial-resistant organisms. Given the clear differences in infection risk and outcome, and availability of risk-adaptive algorithms, the standard of care should move from the 'one-size-fits-all' to a more personalized model taking into account an

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KEY POINTS

- CDRs are available to assist in the risk stratification of children with fever and neutropenia; however, the true clinical, psychosocial, and economic impact of this model of care is unknown.
- Antibiotic administration within 60 min has been shown to improve outcome, although further research is required to quantify the impact in high and low-risk cohorts.
- Infection with antibiotic-resistant bacteria is associated with poor outcome and strategies to predict and optimize management of this emerging threat are urgently required.
- A consensus guideline for paediatric fever and neutropenia research is available and may help reduce some of the heterogeneity between studies that limit our interpretation and implementation of results.

individual's probability of infection, sepsis, and response to treatment.

Risk stratification is the standard of care in the treatment of many paediatric malignancies. Risk-adapted treatment intensity based upon extent of disease, molecular markers, and response to therapy is thought to be an important contribution to improvements in 5-year survival to around 80% [6]. Detailed algorithms guide when to start and stop a treatment, as well as provide options for poor response, or 'resistance' to standard therapy. Despite these innovations in cancer treatment, similarly sophisticated fever and neutropenia treatment algorithms are not available. This is however, not for want of trying, as there has been an extensive quantity of research focused on the cause, biology, risk factors, prevention, and treatment for fever and neutropenia in children [7]. Unfortunately, because of inconsistencies in outcomes that are collected and reported, our ability to compare, contrast, and combine results is limited and may, in part, explain why some advances in fever and neutropenia research have not been translated into practice.

This review will summarize publications, since 2013, that focus on improving the management of fever and neutropenia in children with cancer. A review of publications prior to 2013 is available elsewhere [8].

METHODS

MEDLINE was searched via the PubMed interface using the search terms [(fever or febrile) and (neutropenia or neutropenic) and (child or children or pediatric or paediatric)] and restricted to articles published since 1 January 2013. The search date was 31 May 2015. A total of 249 articles were screened and 16 were included exploring the following themes: standardizing paediatric fever and neutropenia research [7,9▪▪]; defining fever and neutropenia [9▪▪,10▪]; risk stratification [3,11,12▪▪,13]; and time to antibiotics [14▪,15▪,16–21]. Recent publications addressing the emerging threat of antibiotic resistance and its relevance to children with fever and neutropenia are also discussed [22,23,24▪,25,26].

STANDARDIZING PAEDIATRIC FEVER AND NEUTROPENIA RESEARCH

A consensus set of core variables and outcomes that should be measured and reported, as a minimum, in all paediatric fever and neutropenia studies is now available [9▪▪]. This is the first time a paediatric-specific fever and neutropenia research framework has been developed [7]. The authors hypothesize that its application will reduce heterogeneity between clinical studies, limit the impact of reporting bias, and lead to research that is more likely to have outcomes that are relevant to healthcare providers and to patients and their families. Using the Delphi method, a 45-member international panel of clinicians, pharmacists, researchers, and patient representatives completed four sequential surveys exploring core outcomes and definitions specific to paediatric fever and neutropenia research. With a response rate of up to 96%, consensus was achieved on a set of eight core variables and 10 core outcomes as outlined in Table 1. Consensus was also achieved on definitions for the 10 core outcomes.

DEFINING FEVER AND NEUTROPENIA

A consensus definition for 'fever' and 'neutropenia' was unable to be achieved using the Delphi method [9▪▪], which is not surprising given the variety different definitions that are used in both clinical and research settings. Regarding fever, 32% of the Delphi panel agreed with the definition 'a temperature greater than 38.5°C (101.3°F) once or greater than 38.0°C (100.4°F) on two or more occasions during a 12-h period.' Agreement for three other commonly used definitions ranged from 14 to 19% and a further three definitions were proposed. Agreement for a 'neutropenia' definition was slightly higher, with 51% in favour of 'an absolute neutrophil count less than 500/mm^3 or greater than 500 but less than 1000/mm^3 with expected decline to less than 500/mm^3 in the next 48 h.'

Moving from expert opinion to evidence, there is only one prospective study that has addressed the clinical impact of varying definitions for fever

Table 1. Core variable and outcome set that should be measured and reported in all paediatric fever and neutropenia studies (refer to original paper for corresponding definitions) [9▪▪]

Core variable set
Age
Diagnosis
Disease status
Chemotherapy intensity
Antibacterial and antifungal prophylaxis
Central venous catheter
Prior stem cell transplant
Core outcome set
Bacteremia
Clinically documented infection
Microbiologically documented infection
Unexplained fever
Sepsis, severe sepsis, and/or septic shock
ICU admission
Serious medical complication
Infection-related mortality
All cause 30-day mortality
Relapse of primary infection

[10▪]. In this single-centre study routinely using a definition of 39.0°C, the virtual application of a lower limit (37.5–38.9°C) led to earlier fever and neutropenia diagnosis (median, 4.5 h), and to 53 additional fever and neutropenia diagnosed. In 51 (96%) of these additional episodes, spontaneous defervescence without specific therapy was observed in reality. The study was not powered to assess the question of safety of the 39.0°C fever definition, and it is unclear how these single-centre results translate to other centres and if, or how, they should inform a consensus definition.

RISK STRATIFICATION

The incorporation of a validated and robust paediatric fever and neutropenia CDR into practice should enable children to receive more or less intense a high-risk CDR therapy according to their risk of severe infection or other adverse outcomes. An overview of risk stratification, including a review of the efficacy and safety of outpatient management and oral antibiotic administration for low-risk fever and neutropenia, is available [3]. The review discusses potential benefits of reduced intensity treatment for low-risk patients, including improved quality of life for the child and their family, decreased treatment-related toxicities, and reduced exposure to nosocomial infections, including multiresistant organisms as well as considerably reduced health costs. Although not specifically addressed in this review, children identified as high risk may benefit from early and targeted additional supportive care measures and heightened vigilance so as to avoid clinical deterioration and ICU admission.

In 2012, an international paediatric fever and neutropenia guideline panel recommended that centres adopt a validated risk stratification strategy and incorporate it into routine clinical management (level 1C) [27]. Since publication of this guideline, as well as an updated systematic review in 2012 that identified a total of 25 paediatric fever and neutropenia CDRs, no new rule has been formally derived [28]. However, validation of a high-risk CDR [11], a review of methodological quality of 12 existing CDRs [12▪▪], and a study investigating an individual risk factor identified in previously published CDRs are recently available [13].

A CDR is a clinical tool that quantifies the individual contributions that various components of the history, physical examination, and laboratory results make toward the diagnosis, prognosis, or likely response to treatment. Although there are four key components to CDR development (Fig. 1), most investigators stop short at internal validation (i.e., in the same population as the derivation study) resulting in the publication of CDRs with overestimated diagnostic performance [12▪▪,28]. Before a CDR can be implemented into practice it must undergo evaluation in a population external to the original derivation data set to ensure it is well tolerated, reliable, and reproducible. Once we know a CDR accurately predicts outcome, formal

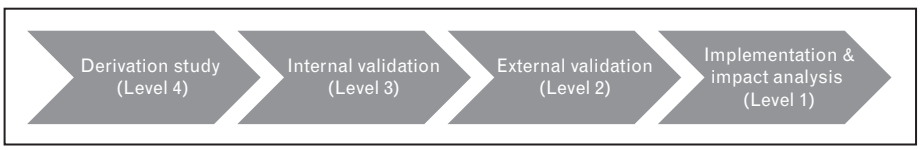

FIGURE 1. Evidence-based medicine working group stages of clinical decision rule development (and corresponding level of evidence). Adapted from [12▪▪].

implementation studies will inform us of the actual impact of the rule, be it clinical, psychosocial, or economic, and may even help drive uptake and sustainability.

The methodological quality of CDRs intended to identify low-risk fever and neutropenia and influence management has recently been assessed in a systematic review [12▪▪]. Seventeen criteria recommended by the evidence-based medicine working group were used to analyse 12 CDRs. The authors summarized these criteria into six key components necessary to achieve the highest level of evidence, including prospective study design; reproducible external to derivation study; clearly defined predictive variables; well defined, clinically significant, and reproducible outcomes; statistical methods described; and the rule must be clinically sensible. Results highlight variable compliance with methodological criteria for CDR development. Notably, the criteria met least often were that the rule 'made clinical sense' and that the variables and the CDRs were 'reproducible.' Only one CDR, developed in South America, met all methodological criteria. It is also the only rule that has undergone prospective medico-economic impact analysis, and was therefore assigned level I evidence. Unfortunately, this rule was not reproducible in Europe, so its clinical utility outside South America is unclear [12▪▪].

An additional validation study of a CDR designed to predict severe sepsis not clinically apparent during the first 4 h of hospitalization in children with fever and neutropenia has been published [11]. Unlike the majority of fever and neutropenia CDRs that have focused on the identification of children at low risk of severe infection, this rule seeks to predict severe sepsis in high-risk fever and neutropenia, and is the first time such a rule has been validated. Factors identified in the derivation study that were independently associated with late onset severe sepsis (including age >12 years, serum C-reactive protein >90 mg/l, and IL-8 > 200 pg/ml) remained significant in the validation set. However, there was a wide difference in ability of all three factors to predict severe sepsis (46% in validation versus 76% in derivation). Furthermore, as the validation population was from the same unit as the derivation set, it is unclear how these results translate to other centres.

There are two fever and neutropenia CDRs that include haemoglobin as a predictor of outcome with conflicting results [28]. In Switzerland, high haemoglobin (>90 g/l) independently predicted severe bacterial infection, while in Brazil, low haemoglobin (<70 g/l) independently predicted severe infectious complications [13]. The unexpected association identified in the former study was recently subject to further analysis [13]. The authors concluded that dehydration, but not medical complications requiring recent transfusion (such as haemolysis, blood loss, suppressed erythropoiesis, and acute transfusion reaction), contributed to the higher than expected haemoglobin levels observed in patients with severe infection. They also found that the association was U-shaped with moderate anaemia associated with the lowest risk of severe infection, whereas both severe anaemia (indicative of severe myelosuppression) and mild/no anaemia (perhaps indicative of dehydration) were associated with a higher risk. These results extend our understanding of ability of haemoglobin to predict outcome as well as the potential impact of external factors such as dehydration on validity of results.

TIME TO ANTIBIOTICS

In addition to predicting the risk of adverse events, recent work has addressed simple modifications in practice that have the potential to improve overall results. There are two studies in children with fever and neutropenia that investigate the impact of time to antibiotics (TTA) on clinical outcome, both of which are from high-income countries [14▪,15▪]. In a retrospective study in North America, 29.9% of children with TTA greater than 60 min were admitted to the ICU compared with 12.6% in the TTA less than 60-min cohort ($P = 0.003$) [15▪]. The study also showed a nonsignificant trend toward higher mortality in children who were administered antibiotics after 60 min. There was no difference in hospital length of stay (LOS). In a larger North American study, albeit also retrospective, TTA greater than 60 min was significantly associated with 'adverse outcome,' a composite measure defined as in-hospital mortality, admission to ICU or 40 ml/kg fluid bolus requirement within 24 h of presentation [14▪].

No paediatric fever and neutropenia study has investigated the effect of TTA according to severity of presenting symptoms, or stratified children according to risk of severe infection or serious medical complication. Outside of fever and neutropenia, the data for TTA are most convincing in the setting of severe sepsis with results of a landmark study in adult patients revealing every hour of delay in antibiotic administration was associated with an average decrease in survival of 7.6% [29]. Based on this, it is conceivable that children with high-risk fever and neutropenia would benefit most from early therapy, although further research is required to quantify the impact of TTA in high and low-risk cohorts.

A target TTA of 60 min for children presenting with fever and neutropenia has been adopted as a standard of care in many centres, although few have managed to consistently achieve this. There has been one audit [16] and six quality improvement initiatives [15▪,17–21] published since 2013 addressing the issue. Baseline data from the quality improvement initiatives revealed that the proportion of patients that received antibiotics within the recommended 60 min ranged from 2 to 63%, with median TTA as high as 154 min in one study [18,20]. Using mixed methodology, including audit and focus group meetings, four studies identified specific barriers to timely administration of antibiotics (Table 2), the most common of which was a delay in accessing the central line [15▪,17,19,21].

Published interventions designed to reduce TTA in children with fever and neutropenia presenting to the emergency department are summarized in Table 2. Following implementation of various combinations of these interventions, a significant reduction in TTA was observed across all studies [15▪,17–21]. The coordinated efforts of multidisciplinary teams, standardized fever and neutropenia triage systems and management algorithms, and comprehensive staff and patient education campaigns were acknowledged as key drivers of change. Three algorithms recommended antibiotic administration prior to neutropenia confirmation in an attempt to eliminate antibiotic prescription delay [17–19], with only one study describing a coordinated approach with the laboratory to achieve complete blood count analysis in as early as 10 min [15▪]. The latter avoiding the unnecessary administration of antibiotics to non-neutropenic patients, which was as high as 52% in one study [19].

Table 2. Barriers to time to antibiotics <60 min and corresponding interventions

Barriers	Interventions
Recognition of FN	Standardized triage category and treatment pathway for all children with cancer presenting with fever
	Patients alert card to notify staff they are at risk of FN and/or have a central line
CVAD access	ED staff education:
	CVAD access practical skills workshop and written and online resources
	Patient/family education:
	Apply topical anesthetic cream to Port prior to leaving home
	Allow the ED staff to obtain CVAD access rather than requesting specific oncology nurses
Ordering blood tests	Standardized pathology order set for all FN patients
	Nurse initiated CVAD access and blood tests
Antibiotic availability	All FN antibiotic options available in the ED
	Preprepared antibiotics at set doses available in ED
Antibiotic administration	First dose antibiotic prior to CBC result and oncology consult
	Nurse-initiated antibiotics

CBC, cell blood count; CVAD, central venous access devices; ED emergency department; FN, fever and neutropenia. Adapted from [17,20–23,24▪].

ANTIBIOTIC RESISTANCE

Infection with antibiotic-resistant bacteria has emerged as a serious threat to children with fever and neutropenia [22,23]. Of particular concern are multidrug-resistant bacteria that render the commonly prescribed empiric fever and neutropenia antibiotics ineffective. Although there are no recently published studies that have investigated the clinical impact of antibiotic-resistant infection, earlier reports indicate these infections do negatively impact prognosis. In particular, a significant association with prolonged hospital LOS, ICU LOS, and ventilation requirements has been described [24▪,25]. Antibiotic resistance has also been shown to increase the risk of infection-related and all-cause mortality [24▪,30,31]. The rates quoted in some of these studies were as high as historic reports of mortality in patients with cancer treated prior to the routine availability and use of empiric antibiotics for fever and neutropenia [32].

In a review of factors associated with antibiotic-resistant Gram-negative bacteremia, hospital admission for at least 48 h was shown to be significant [24▪]. Although the review identified only one paediatric study that showed recent antibiotic exposure was also an independent risk factor for antibiotic-resistant bacteremia, the association is well described in the adult haematology and oncology population [33]. Furthermore, in three studies, the proportion of gram-negative bacteria resistant to empiric antibiotic regimen used at each centre increased significantly over time and may, in part, be explained by repeated exposure to these agents.

In an era of increasing antimicrobial resistance, it is incumbent on institutions that offer curative cancer treatments to similarly offer strategies to monitor, prevent, and appropriately manage these infections. At a minimum, local epidemiology and resistance rates should guide empiric antibiotic selection as outlined in a recent Italian study [23].

A comprehensive review of the current infection-control issues facing patients with haematological malignancy is available. The authors of this review summarize the latest recommendations for infection control bundles of care as well as antibiotic options for multidrug-resistant bacteria [26]. The importance of integrated multidisciplinary antimicrobial stewardship (AMS) programmes is also emphasized with a practical framework for implementation, based on guidelines from the Fourth European Conference on Infections in Leukaemia (ECIL-4), described. Clinical outcome data of the benefits of AMS are beginning to emerge with a study in adults showing patients with fever and neutropenia treated according to AMS recommendations had a relative risk reduction in 28-day mortality of 64% compared with cases receiving antimicrobial treatment nonadherent to AMS recommendations [34].

No paediatric study has specifically addressed the clinical impact of modifications to empiric fever and neutropenia antibiotic based on underlying risk of infection with antibiotic-resistant bacteria. Given the association with poor outcome, this is an area where further research is urgently required.

CONCLUSION

A risk-stratified approach to care is recommended for children with fever and neutropenia. Although many CDRs are available to assist in risk stratification, further research is required to refine exactly which children would benefit most from emerging management strategies such as target TTA. In the era of increasing antimicrobial resistance and paucity of new antibiotic agents in the pipeline, research should also be directed toward the early predication and prevention of antibiotic-resistant infections, and management algorithms adapted according to local epidemiology. Finally, to encourage uptake and sustainability of a risk-adapted model of care for children with fever and neutropenia, the clinical, psychosocial, and economic impact of currently available CDRs should be formally investigated using a recommended research framework [9▪▪,12▪▪].

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Mueller EL, Walkovich KJ, Mody R, *et al.* Hospital discharges for fever and neutropenia in pediatric cancer patients: United States. BMC Cancer 2015; 15:388.
2. ▪ Mueller EL, Sabbatini A, Gebremariam A, *et al.* Why pediatric patients with cancer visit the emergency department: United States. Pediatr Blood Cancer 2015; 62:490–495.

Large study based on nation-wide administration data that defines the burden of fever and neutropenia on emergency department presentations and hospital admission.

3. Henry M, Sung L. Supportive care in pediatric oncology: oncologic emergencies and management of fever and neutropenia. Pediatr Clin North Am 2015; 62:27–46.
4. Bate J, Gibson F, Selwood K, *et al.* A reaudit of current febrile neutropenia practice in UK paediatric oncology centres prior to implementation of NICE guidance. Arch Dis Child 2013; 98:315–316.
5. Mueller EL, Walkovich KJ, Yanik GA, Clark SJ. Variation in management of fever and neutropenia among pediatric patients with cancer: a survey of providers in Michigan. Pediatr Hematol Oncol 2015; 32:331–340.
6. Gatta G, Botta L, Rossi S, *et al.* Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5: a population-based study. Lancet Oncol 2014; 15:35–47.
7. Haeusler GM, Phillips RS, Lehrnbecher T, *et al.* The reporting of outcomes in studies of fever and neutropenia in children with cancer: time for consensus. Pediatr Blood Cancer 2013; 60:1563–1564.
8. Ammann RA, Tissing WJ, Phillips B. Rationalizing the approach to children with fever in neutropenia. Curr Opin Infect Dis 2012; 25:258–265.
9. ▪▪ Haeusler GM, Phillips RS, Lehrnbecher T, *et al.* Core outcomes and definitions for pediatric fever and neutropenia research: a consensus statement from an international panel. Pediatr Blood Cancer 2015; 62:483–489.

International consensus recommendations for core outcomes and definitions for paediatric fever and neutropenia research.

10. ▪ Ammann RA, Teuffel O, Agyeman P, *et al.* The influence of different fever definitions on the rate of fever in neutropenia diagnosed in children with cancer. PLoS One 2015; 10:e0117528.

The first prospective study to address different fever definitions on clinical outcome in children with cancer.

11. Santolaya ME, Alvaréz AM, Aviles CL, *et al.* Prospective validation of a risk prediction model for severe sepsis in children with cancer and high-risk febrile neutropenia. Pediatr Infect Dis J 2013; 32:1318–1323.
12. ▪▪ Delebarre M, Macher E, Mazingue F, *et al.* Which decision rules meet methodological standards in children with febrile neutropenia? Results of a systematic review and analysis. Pediatr Blood Cancer 2014; 61:1786–1791.

A systematic review of paediatric fever and neutropenia CDR focusing on methodological quality of derivation, validation, and impact analysis studies. Rules achieving level 1 evidence are highlighted.

13. Ammann RA, Niggli FK, Leibundgut K, *et al.* Exploring the association of hemoglobin level and adverse events in children with cancer presenting with fever in neutropenia. PLoS One 2014; 9:e101696.
14. ▪ Fletcher M, Hodgkiss H, Zhang S, *et al.* Prompt administration of antibiotics is associated with improved outcomes in febrile neutropenia in children with cancer. Pediatr Blood Cancer 2013; 60:1299–1306.

One of the first studies to explore the impact of time to antibiotics in children with cancer and fever and neutropenia.

15. ▪ Salstrom JL, Coughlin RL, Pool K, *et al.* Pediatric patients who receive antibiotics for fever and neutropenia in less than 60 min have decreased intensive care needs. Pediatr Blood Cancer 2015; 62:807–815.

One of the first studies to explore the impact of time to antibiotics in children with cancer and fever and neutropenia.

16. Cox A, Bradford N. Management of febrile neutropenia in pediatric oncology across Queensland, Australia: a retrospective review on variations between locations. J Pediatr Oncol Nurs 2014; 31:28–33.
17. Vedi A, Pennington V, O'Meara M, *et al.* Management of fever and neutropenia in children with cancer. Support Care Cancer 2015; 23:2079–2087.
18. Cash T, Deloach T, Graham J, *et al.* Standardized process used in the emergency department for pediatric oncology patients with fever and neutropenia improves time to the first dose of antibiotics. Pediatr Emerg Care 2014; 30:91–93.
19. Cohen C, King A, Lin CP, *et al.* Protocol for reducing time to antibiotics in pediatric patients presenting to an emergency department with fever and neutropenia: efficacy and barriers. Pediatr Emerg Care 2015. [Epub ahead of print]
20. Jobson M, Sandrof M, Valeriote T, *et al.* Decreasing time to antibiotics in febrile patients with central lines in the emergency department. Pediatrics 2015; 135:e187–e195.
21. Dobrasz G, Hatfield M, Jones LM, *et al.* Nurse-driven protocols for febrile pediatric oncology patients. J Emerg Nurs 2013; 39:289–295.

22. El-Mahallawy H, Samir I, Abdel Fattah R, *et al.* Source, pattern and antibiotic resistance of blood stream infections in hematopoietic stem cell transplant recipients. J Egypt Natl Canc Inst 2014; 26:73–77.

23. Castagnola E, Caviglia I, Pescetto L, *et al.* Antibiotic susceptibility of Gram-negatives isolated from bacteremia in children with cancer. Implications for empirical therapy of febrile neutropenia. Future Microbiol 2015; 10:357–365.

24. Haeusler GM, Levene I. What are the risk factors for antibiotic resistant Gram-
■ negative bacteraemia in children with cancer? Arch Dis Child 2015; 100:895–898.

Systematic overview of the prediction of drug-resistance at first presentation of fever and neutropenia.

25. Haeusler GM, Mechinaud F, Daley AJ, *et al.* Antibiotic resistant Gram-negative bacteraemia in paediatric oncology patients: risk factors and outcome. Paediatr Infect Dis J 2013; 32:723–726.

26. Ruhnke M, Arnold R, Gastmeier P. Infection control issues in patients with haematological malignancies in the era of multidrug-resistant bacteria. Lancet Oncol 2014; 15:e606–e619.

27. Lehrnbecher T, Phillips R, Alexander S, *et al.* Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. J Clin Oncol 2012; 30:4427–4438.

28. Phillips RS, Lehrnbecher T, Alexander S, *et al.* Updated systematic review and meta-analysis of the performance of risk prediction rules in children and young people with febrile neutropenia. PLoS One 2012; 7:e38300.

29. Kumar A, Roberts D, Wood KE, *et al.* Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006; 34:1589–1596.

30. El-Mahallawy HA, El-Wakil M, Moneer MM, Shalaby L. Antibiotic resistance is associated with longer bacteremic episodes and worse outcome in febrile neutropenic children with cancer. Pediatr Blood Cancer 2011; 57:283–288.

31. Caselli D, Cesaro S, Ziino O, *et al.* Multidrug resistant Pseudomonas aeruginosa infection in children undergoing chemotherapy and hematopoietic stem cell transplantation. Haematologica 2010; 95:1612–1615.

32. Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 1966; 64:328–340.

33. Trubiano JA, Worth LJ, Thursky KA, Slavin MA. The prevention and management of infections due to multidrug resistant organisms in haematology patients. Br J Clin Pharmacol 2015; 79:195–207.

34. Rosa RG, Goldani LZ, dos Santos RP. Association between adherence to an antimicrobial stewardship program and mortality among hospitalised cancer patients with febrile neutropaenia: a prospective cohort study. BMC Infect Dis 2014; 14:286.